Obesity, adipokines, and prostate cancer (Review)

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Abstract. Prostate cancer, the third most common cancer in men worldwide, varies substantially according to geographic region and race/ethnicity. Obesity and associated endocrine variation are foremost among the risk factors that may underlie these regional and ethnic differences. The association between obesity and prostate cancer incidence is complex and has yielded inconsistent results. Studies that have linked obesity with prostate cancer mortality, advanced stage disease, and higher grade Gleason score, however, have produced more consistent findings, indicating that obesity may not necessarily increase the risk of prostate cancer, but may promote it once established. Additionally, metabolic syndrome, which includes disturbed glucose metabolism and insulin bioactivity, may also be associated with prostate carcinogenesis. Adipokines, defined as biologically active polypeptides produced by adipose tissue, have been linked with a number of carcinogenic mechanisms, including angiogenesis, cell proliferation, metastasis, and alterations in sex-steroid hormone levels. A number of emerging studies have implicated the role of adipokines in prostate carcinogenesis. This review explores the specific roles of several adipokines as putative mediating factors between obesity and prostate cancer with particular attention to leptin, interleukin-6 (IL-6), heparin-binding epidermal growth factor-like growth factor (HB-EGF), vascular endothelial growth factor (VEGF) and adiponectin.

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1. Introduction

Prostate cancer is the third most common cancer in men worldwide and occurs most commonly in the United States and Canada, and northwestern Europe, but is uncommon in Asian countries and South America (1). An epidemiologic study of 12 countries of the European Union shows a clear north-south gradient in prostate cancer incidence and mortality, which has persisted over time, with particularly high figures for England and Wales, and low rates in Italy, Spain, and Portugal (2). Although Asian men have the lowest incidence and mortality rates of prostate cancer worldwide, these have been showing a rapid increase over the past 20-30 years, possibly a consequence, of a shift in dietary practices towards a more western pattern, and the associated increase in obesity (3). Obesity, adiposity and the associated endocrine factors may contribute substantially to such geographic and ethnic differences in prostate cancer incidence worldwide and will be the focus of this review (1).

During the earlier stages of the disease, most prostate cancers are dependent for their growth on stimulation by androgenic steroids, and tumor regression can be obtained by surgical and medical suppression of androgen action (4,5). However, a point is eventually reached when a proportion of the cancer cells are no longer dependent on androgens and renewed progression takes place. This situation occurs in part when tumor cells emerge which both synthesize and secrete polypeptide growth factors such as epidermal growth factor, transforming growth factor-α, and insulin-like growth factor-1 (IGF-1), and possess the corresponding cell membrane receptors: the resulting autocrine stimulation is typical of androgen-independent prostate cancer cells (6).

In addition to inducing phenotypic changes in the prostate cancer cell, the immediate microenvironment provided by the host tissues may play an important role in the growth and metastasis of prostate cancers (5). There are multiple modes of action for this host-tumor cell relationship; in this review we will develop the concept that one such mechanism arises from the metabolic consequences of obesity and the metabolic syndrome, and in particular the endocrine and paracrine activities of cytokines synthesized by adipose tissue.

2. Obesity and the metabolic syndrome

Obesity and body fat distribution. Studies assessing the association between obesity and prostate cancer have yielded inconsistent results. Several investigations found an increased risk of prostate cancer among obese and overweight men (7-12), including a large prospective study from Sweden which involved 134,000 construction workers (10). Other studies, however, indicated little or no association (13-17), among which were two of prospective design with 9,000 and 47,781 men, respectively (13,15).

More consistent results have been obtained for patients with established disease, where obesity was found to be predictive of a poor prognosis (10,18-20), and to be associated with higher tumor grade and stage (11,19-25), indicative of more aggressive cancer, and with more advanced disease at the time of diagnosis, defined by invasion through the prostatic capsule, involvement of adjacent tissues and lymph glands and, perhaps, distant metastases (9,22,25). A large study by Kane *et al* (26) involving 2,952 prostate cancer patients showed a positive correlation between BMI values in those categorized as being overweight to very obese (25 kg/m^2 or more) and tumors with a poor prognosis as based on the calculated tumor volume and the pretreatment prostatic specific antigen level. These observations suggest that the relationship between obesity and prostate cancer is the result of its biological effects in promoting an aggressive phenotype rather than the trans-formation of the prostatic epithelium *per se*.

However, in addition to obesity which is present at the time of prostate cancer diagnosis, a number of investigations have examined the significance of body weight earlier in life on subsequent prostate carcinogenesis. A study from Italy found a positive association between prostate cancer risk and a high BMI at age 30 years (27), and the Netherlands Cohort Study (28) gave results which showed the BMI at 20 years of age to be positively related to risk. Another prospective study, from Scotland, with a mean follow-up of 41 years, found that there was an increased risk for subsequent prostate cancer death for men in the highest BMI category at age 20-22 years, few of whom were obese (29). In contrast to these results, Robinson *et al* (30) performed a case-control study of prostate cancer in African-American and white American men in relation to the presence of obesity when they were less than 30 years of age and found evidence of a reduced risk in those who had a BMI of 30 kg/m^2 or higher.

The distribution of body fat, as opposed to adiposity assessed by the BMI, has been studied extensively in breast cancer; most investigators used the ratio of the waist to hip circumference (WHR) for this purpose, and the majority, but not all, concluded that a high WHR, indicative of upper body obesity, is associated with an increase in postmenopausal breast cancer and, perhaps, with a poor prognosis (31). Although the amount of data available for evaluation is limited, upper body or visceral obesity has also been found to correlate with increased prostate cancer risk. In a case-control study from China (17) a high WHR was related to an excess risk; interestingly, there was no relationship between risk and the BMI in this study. Actually, while providing some useful information in epidemiological studies, the WHR is a relatively crude method of assessing body fat distribution because it does not distinguish between deep abdominal or visceral fat and sub-cutaneous fat deposits. Von Hafe *et al* (12) used computerized tomography to measure the abdominal fat directly in a case-control study, and showed that the prostate cancer patients had a higher mean visceral fat area and visceral to subcutaneous fat area ratio than controls: the calculated prostate cancer risk associated with these indicators of visceral adiposity had odds ratios of 4.6 and 6.0, respectively.

Metabolic syndrome. The metabolic (or insulin resistance) syndrome is characterized by a cluster of biochemical abnormalities and associated clinical conditions, not all of which are necessarily present in a given case, but which include disturbed glucose metabolism and insulin bioactivity resulting in hyperglycemia and hyperinsulinemia, dyslipidemia (hyper-triglyceridemia and low levels of HDL cholesterol), hyper-tension, and type 2 diabetes (32). Central obesity is often present, but the syndrome does occur in its absence; lean individuals exhibit a wide range of insulin sensitivity, and may have levels as low as those of obese insulin-resistant subjects (33). The mechanisms underlying this syndrome are not completely understood, but insulin resistance associated with obesity, sedentary lifestyle, energy intake, and genetic pre-disposition are part of the etiology (32,33). Since prostate cancer has been linked to many of the component endocrine characteristics of metabolic syndrome, investigators have recently begun assessing its association with prostate cancer. The metabolic syndrome is a common clinical condition in countries with western dietary patterns and a high incidence of obesity; in the United States its prevalence in the adult population has been estimated to be approximately 25% (32).

The case-control study of Chinese men performed by Hsing *et al* (17), which showed that a high WHR, but not the BMI, was positively associated with prostate cancer risk, was extended to include an examination of several serum constituents, including the insulin concentration (34). After adjustment for the BMI and WHR there was a highly significant association between higher serum insulin levels and increased risk of prostate cancer. However, there was also an interaction between the WHR and the serum insulin. Men in the highest tertiles of both WHR and insulin had 8.55 times the prostate cancer risk of men in the two lower tertiles; those with the lowest tertile of WHR, but the highest tertile of insulin had 4.30 times the risk. In a further study by these same investigators (35), the homeostasis model assessment was used to evaluate insulin resistance in prostate cancer patients and controls; the results showed that the men in the highest tertile of insulin resistance were at an increased cancer risk, and conversely, a high degree of insulin sensitivity was associated with reduced risk. Again, there was an interaction between high WHR and insulin resistance. Laukkanen *et al* (36), in a prospective study of prostate cancer in Finland, reported that men with metabolic syndrome were nearly two times more likely to develop prostaste cancer than those without. This association was stronger in overweight men with a BMI >27 kg/m^2 (adjusted relative risk, 3.0; 95% CI 1.2-3.7) than in lighter men (adjusted relative risk, 1.8; 95% CI 0.7-4.7). These findings were not attenuated by adjusting for potential lifestyle factors such as alcohol consumption, smoking, physical fitness, or a number of dietary factors.

Features of the metabolic syndrome have also been associated with the occurrence of larger tumors at the time of prostate cancer diagnosis. In the study by Hammarsten and Hogstedt (37) patients with later stage prostate cancer were found to have relatively high plasma insulin levels, and more likely than those with early tumors to be hypertensive and dyslipidemic, with elevated serum triglycerides and reduced HDL-cholesterol levels. Also, they were more obese, with higher WHRs, and, particularly the large waist circumference which is so often an anthropometric feature of the metabolic syndrome.

Mechanisms. The progression of prostatic carcinogenesis is believed to involve epithelial-mesenchymal/stromal interaction which takes place with the participation of both testosterone and estradiol (38), but the precise roles of these two classes of steroid hormones is not entirely clear. However, estrogens alone, or in conjunction with androgens do induce aberrant prostate growth and neoplastic transformation (39).

Obesity might facilitate prostate carcinogenesis and progression during the phase of hormone dependence through its enhancement of estrogen biosynthesis. This occurs due to an increase in the activity of aromatase which is located in the accumulated adipose tissue; there is an age-related and adiposity-related increase in the aromatization of testosterone to estradiol (40); alternatively, the loss of testosterone could be expected to exert a suppressive effect on prostate cancer development. The situation is rendered even more complex by the possibility that in the presence of the metabolic syndrome the increase in insulin bioactivity might produce up-regulation of testosterone production by insulin (41); in addition, the bioavailability of the androgen is enhanced by an obesity and insulin-related reduction in sex hormone-binding globulin (SHBG) synthesis (41,42).

In recent years there has been increasing recognition that adipose tissue functions as an endocrine and paracrine organ, and exerts widespread biological effects by the production of cytokine-like polypeptide factors. Several of these have been studied for their contribution to prostate cancer development and progression, both during the androgen-dependent and androgen-independent phases of growth and metastasis.

3. Adipose tissue-derived cytokines

A variety of biologically active factors are secreted by the fat storage cells (the adipocytes) and supporting stromal cells, and by other cell types, particularly macrophages, which infiltrate the adipose tissue and accumulate in increased numbers in association with obesity (43). The hormone-like polypeptides produced in the adipose tissue are termed adipokines. Those synthesized specifically by the adipocytes were first designated as adipocytokines by Matsuzawa *et al* (44). Several, including leptin, heparin-binding epidermal growth factor-like growth factor (HB-EGF), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and adiponectin, are becoming increasingly recognized for their multiple effects on the bio-logical behavior of tumor cells. Adipokines circulate in the blood, and, like steroid hormones, they can exert their bio-logical actions on target cells by classical ligand-receptor endocrine mechanisms. In addition, like the inflammatory cytokines, they can operate at the local level through paracrine and autocrine pathways.

The plasma concentrations of leptin (45,46), HB-EGF (47), and IL-6 (48) are all elevated in obese men. Serum VEGF concentrations have been reported to be positively correlated with the visceral fat mass (49) and VEGF stimulates expansion of the capillary network in fat tissue which is essential for increasing adiposity (50,51). In contrast, plasma adiponectin levels decrease with increasing adiposity (52,53). A number of the adipokines are involved in the regulation of insulin activity, and their production is altered in the metabolic syndrome. Leptin can disrupt insulin signaling (54); plasma leptin and insulin show a positive correlation, and hyper-leptinemia, as well as hyperinsulinemia, is a biological feature of both type 2 diabetes and the metabolic syndrome (55,56). Conversely, adiponectin promotes insulin sensitivity in target tissues, and opposes the development of type 2 diabetes (57); hypoadiponectinemia is associated with the metabolic syndrome (58). The biological properties of leptin suggest its involvement in breast cancer cell growth, invasion, and metastasis, and in tumor-related neovascularization or angio-genesis (31,59).

4. Leptin and prostate cancer

Epidemiological studies and circulating leptin concentrations. Equivocal results have been obtained from the investigation of plasma leptin levels in prostate cancer patients. Hsing *et al* (34), in their case-control study of Chinese men, found that although those with serum insulin levels in the highest tertile had an increased prostate cancer risk, the association between serum leptin concentrations and risk was not statistically significant.

Stattin *et al* (60) originally reported that the results from a nested case-control analysis showed that moderately, but curiously not markedly, elevated plasma leptin concentrations were related to an increased risk of prostate cancer. However, a second study by this same group failed to confirm the relationship (61), and neither has the work of other investigators (62,63). Despite the lack of any convincing evidence that high plasma leptin levels are related to prostate cancer risk, there are indications from some (64-66), but not all (67), studies that the same abnormality is predictive of high grade disease and more advanced tumors. Certainly, the results of investigations of leptin and prostate cancer cell biology support such a relationship.

Prostate cancer cell biology. Leptin receptor protein was detected by immunohistochemical staining with an antibody reactive to the long and short isoforms in normal human prostatic cells, intraepithelial neoplasia, and prostate cancer epithelium (60) and the mRNAs for both forms of the receptor were demonstrated in the androgen-independent DU145 and PC-3 human prostate cancer cell lines (68). In cell culture experiments, exogenous leptin stimulated the growth of these two lines (68-70), but the androgen-dependent LNCaP prostate cancer cell line, although it possesses the two leptin receptor isoforms, showed no mitogenic response to the ligand (69).

The proliferative response of DU145 and PC-3 prostate cancer cells to leptin was shown to involve phosphatidyl-

inositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) activation (68), and the participation of activated c-Jun NH2-terminal kinase (JNK); the pharmacological inhibition of JNK blocked the proliferative response to leptin (69). It is of particular interest to the present discussion that JNK has been shown to be elevated in animal models of obesity, and to induce insulin resistance (71,72). Yang *et al* (73) showed in a series of human prostate cancer cell lines that there was a strong correlation between the extent of their growth enhancement in the presence of high serum supplementation *in vitro* and serum-inducible JNK activity. Lin *et al* (74) demonstrated that the PI3K pathway is also critical for the survival of androgen-dependent prostate cancer cells by showing that apoptosis of LNCaP cells occurred rapidly in the presence of a PI3K inhibitor, an antiproliferative effect which was attenuated by another adipocytokine, HB-EGF.

5. IL-6 and HB-EGF and prostate cancer

The adipose tissue is a major production site of IL-6 (75,76), although infiltrating macrophages and stromal cells produce most of the IL-6 arising in adipose tissue and only about 10% is synthesized by the adipocytes (76). There is a positive correlation between the serum IL-6 concentration and the BMI (48,75) and the circulating levels are elevated in obesity and insulin resistance (76-78).

The serum IL-6 levels are also increased in some prostate cancer patients, when they are associated particularly with a loss of androgen dependence (79,80), the presence of metastatic disease (81-83), and reduced survival time (84,85). Although these observations are consistent with an IL-6-mediated adverse effect of obesity on prostate cancer outcome, and this cytokine does stimulate the growth of human prostate cancer cell lines *in vitro* (86,87), the synthesis and secretion of the polypeptide by the tumor cells themselves suggests that autocrine stimulation may also contribute to IL-6-mediated growth (86-89). Okamoto *et al* (86) reported that the androgen-dependent LNCaP cell line was much more responsive to culture medium containing added IL-6 than the DU145 and PC-3 cell lines, whereas only the two androgen-independent lines secreted significant endogenously produced levels of the cytokine. The inference from these results is that IL-6, most likely derived from adipose sources, is primarily a paracrine, and perhaps endocrine, growth factor for androgen-dependent prostate cancer cells but that it assumes an auto-crine function of the tumor cells themselves as part of the emergence of androgen independence.

Heparin-binding epidermal growth factor-like growth factor is produced at multiple sites including human adipose tissue. There is an increase in HB-EGF mRNA expression by adipose tissue in obese mice (47), and a positive correlation exists between plasma HB-EGF concentrations and the BMI in humans (90). Like IL-6, exogenous HB-EGF stimulates the growth of cultured human prostate cancer cell lines (91,92) and is produced by the tumor cells, so providing the potential for significant autocrine mitogenic activity (91). The expression of HB-EGF was found to be considerably greater in cell lines that were androgen-independent (92,93) suggesting, as in the case of IL-6, an adipokine-related mechanism for escape of prostate cancer from androgen dependence.

6. Special relationships of adiponectin

Adiponectin is a 30-kDa collagen-like plasma protein which is synthesized exclusively in adipocytes (94). One of the most abundant adipocytokines, it circulates in the blood at a concentration which amounts to 0.05% of the total serum proteins (94). The plasma adiponectin levels, like those of leptin, are higher in women than men (57,95,96). Nishizawa *et al* (95) found in a group of Japanese men that the plasma adiponectin concentration was 34% lower than in women; in parallel experimental studies they showed that castration produced a significant elevation in plasma adiponectin in mature male mice, while the administration of testosterone to both these androgen-deficient animals and intact mice caused a reduction in the secretion of adiponectin from adipose tissue and in the plasma concentration of the adipocytokine.

There are a number of situations other than their opposing actions on insulin signaling, where adiponectin has been shown to have effects which are clearly antagonistic to those produced by leptin. Adiponectin can accelerate the process of apoptosis in hematopoietic cells, for which leptin is mitogenic (97); it induces apoptotic activity by down-regulating *Bcl-2* expression (98). Also, at least under some circumstances it was found to have a similar effect on vascular endothelial cell growth by activating the caspase cascade (99), which contrasts with the *Bcl-2*-inducing, antiapoptotic activity of leptin on these cells (100).

These opposing effects of adiponectin and leptin on various aspects of metabolism and cell biology suggest that, in contrast to leptin, adiponectin may possess anticancer properties which are lost in clinical situations associated with hypoadiponectin-emia. In support of this proposition are reports that sub-normal plasma concentrations of adiponectin are related to increased risks of carcinoma of the breast (101,102), and endometrium (103,104), and in men but apparently not in women, cancer of the colon (105). One of the studies of breast cancer also showed that patients with low adiponectin levels were more likely to have tumors which were large and of high histologic grade (102). A small case-control study performed in Turkey by Goktas *et al* (106) has now extended the relationship between hypoadiponectinemia and cancer to include carcinoma of the prostate. Plasma adiponectin levels were significantly lower in a group of 30 prostate cancer patients than in 41 patients with benign prostatic hyperplasia, and 36 healthy controls. Further, the adiponectin concentrations were inversely correlated with the tumor grade and disease stage. It is important to a discussion of prostate cancer and insulin resistance that although obese men were excluded from this study, and there were no significant differences in the BMI values between the three groups, the plasma insulin levels were higher, and insulin resistance as indicated by the homeostasis model assessment method was greater in the cancer patients, and particularly so in those whose disease had spread beyond the confines of the gland itself.

There have been no published studies to determine if adiponectin has a direct effect, inhibitory or otherwise, on prostate, breast, endometrial, or colon cancer cell proliferation, but Yokota *et al* (98) did report that it suppressed the growth of myelocyte lines and induced apoptosis in myelomonocytic leukemia cell lines. Also, when infused into highly vascularized

mouse fibrosarcomas, adiponectin caused suppression of tumor growth, but here the mechanism was most likely an antiangiogenic effect (99).

7. Angiogenesis in prostate cancer

Angiogenesis is the process by which new blood vessels are formed from preexisting vasculature. Once neoplastic transformation has taken place, and carcinoma *in situ* has formed, angiogenesis-mediated cancer progression may occur by a process of tumor cell proliferation, vascularization of the tumor mass, local invasion, and metastasis to sites remote from the primary tumor (107-109). In clinical studies of prostate cancer, angiogenesis correlated with disease stage and the presence of metastases (110-112), and was shown to occur in those intraepithelial neoplasms (111) and latent carcinomas (113) which exhibited potential for progression to invasive disease.

A high degree of microvessel density, indicative of active angiogenesis, and a relatively high expression of VEGF, were found concurrently in high grade, potentially aggressive, human prostate cancer tissues (112,114-116). Moreover, VEGF expression was further enhanced in tumors that had extended beyond the capsule of the gland, and so gained access to the surrounding adipose tissue (114,115). Increased Plasma VEGF concentrations have also been reported in patients with metastatic prostate cancer compared with those in patients with localized disease and healthy controls (117).

Vascular endothelial cell proliferation and migration *in vitro* and the complete process of angiogenesis *in vivo* are stimulated not only by VEGF, but also by leptin (118,119, reviewed in ref. 31). Heparin-binding EGF-like growth factor is also a potent promoter of angiogenesis; it does not stimulate vascular endothelial cell proliferation directly, but it is an inducer of VEGF expression (120,121), and stimulates endothelial cell migration (120,121), the production of proteolytic enzymes which are essential for the movement of the cells, and their organization into vascular tubes (120-122). Finally, HB-EGF was shown to be angiogenic in *in vivo* models (120,121).

The physiological and pathological significance of IL-6 as a stimulator of angiogenesis is currently undergoing vigorous investigation. Although it was reported to have only weak stimulatory effects on the migration of vascular endothelial cells and their formation of tubular systems *in vitro*, and not to stimulate angiogenesis in the rabbit corneal model (123) more recent experiments showed that IL-6 can induce VEGF expression and promote angiogenesis in a gastric carcinoma model (124), and also stimulate the transcriptional up-regulation of VEGF and VEGF secretion in glioblastoma cells (125). It also induced angiogenesis indirectly by the induction of bFGF expression in an *in vitro* model (126).

Thus, all three of the adipokines discussed in this review whose production from adipose tissue is directly correlated with the BMI exert positive effects on the angiogenic process. Transformed prostatic cells which are initially restricted to the gland itself by the surrounding capsule come under the influence of these adipose tissue-derived angiogenic factors when they invade the retropubic fat pad which will enhance their capacity for further growth and metastasis to the regional lymph nodes and distant sites.

In keeping with its general opposition to the biological activities of leptin, Brakenhielm *et al* (99) reported that adiponectin possesses antiangiogenic properties. In their experiments they showed that, in contrast to leptin and VEGF, adiponectin inhibited the growth of microvascular (capillary) endothelial cells, and their capacity for migration *in vitro*. Furthermore, it suppressed the stimulatory effects of bFGF on microvascular endothelial cell proliferation, and of VEGF on cell migration. *In vivo*, adiponectin inhibited angiogenesis in both the mouse corneal and the chick chorioallantoic membrane models. As noted earlier, Brakenhielm and colleagues also showed that the infusion of adiponectin into highly vascularized mouse fibrosarcomas produced suppression of tumor growth, with an associated reduction in angiogenic activity.

8. Commentary

The relationships between obesity, androgens and leptin are complex, and may contribute to the inconsistencies seen in the reports of studies of obesity and prostate cancer risk. Obesity in men is associated with a reduction in both the plasma total and the free, non-SHBG-bound and biologically active, testosterone levels (40,127); Isidori *et al* (128) found that this decrease in the free testosterone could occur even when there was a concomitant reduction in the plasma SHBG concentration. Obesity in boys is associated with delayed pubertal development, and an obesity-related state of relative hypoandrogenism may explain the finding by Giovannucci *et al* (15) from their large prospective study that although the adult BMI was not related to prostate cancer risk or stage at diagnosis, obese boys were more likely to exhibit a reduced risk of having advanced prostate cancer when the disease was diagnosed in later life.

A somewhat similar result from a case-control study was reported by Robinson *et al* (30), although here obesity was assessed in young adults aged 20-29 years and preadolescent boys. An inverse relationship was found between the BMI and later risk of advanced prostate cancer which was evident in preadolescence, but most pronounced between the ages of 20 and 29 years. It should be noted that if reduced testosterone levels in early life are responsible for producing changes in the prostate gland which mitigate against the subsequent emergence of prostate cancer with an aggressive phenotype, they do so in the presence of an increase in the plasma leptin. However, it may be relevant that, as we saw earlier, leptin only activated JNK and stimulated the growth of androgen-independent human prostate cancer cell lines; there was no effect of leptin on the testosterone responsive LNCaP prostate cancer line (68,69). Thus, we can speculate that the behavior of premalignant or cancerous prostate cells in response to leptin is determined by their androgen dependence and that this, in turn, may contribute to the positive and negative effects reported from different studies of the influence of obesity on prostate cancer.

One additional but related factor may be the degree of obesity present in the study population. Robinson *et al* (30) referenced 7 studies of body size in young adult males and their subsequent risk of prostate cancer and advanced disease; none showed a reduced risk in those with higher BMI values, but rather there was either no effect or a slight increase in

risk. However, as in the case of the young men referred to earlier in the study by Okasha *et al* (29), and in contrast to those examined by Giovannucci *et al* (15) and Robinson *et al* (30) none of the study subjects included individuals with BMI levels in the obesity range, and in consequence any suppressive effect on the plasma testosterone concentrations may have been minimal. In support of this conclusion, it is noteworthy that Robinson *et al* (30) also found a slight increase in the risk of advanced prostate cancer in their subjects with BMI values in the 25-29 range, i.e. overweight but not obese.

The increased risk of prostate cancer and of higher grade and stage which Goktas *et al* (106) reported in association with reduced plasma adiponectin concentrations was not related to higher BMI values and none of the subjects included in this small case-control study were obese. However, it is of special interest that in addition to the subnormal adiponectin levels, progression to high prostate cancer grade was associated with biochemical evidence of sequential increases in insulin resistance and related hyperinsulinemia. This result is consistent with other reports that insulin resistance and other features of the metabolic syndrome are related to increased prostate cancer risk and advanced disease (34-37). Further investigations should be designed to distinguish between a causative role for insulin resistance *per se* in prostate carcinogenesis and expression of the metastatic phenotype, and a primary, specific, effect of hypoadiponectinemia on prostate (and breast and endometrial) cancer biology.

The role of an adipokine as a classical hormone in the growth and metastasis of prostate cancer is best supported by the available evidence in the case of adiponectin. This is the one adipose tissue-derived polypeptide of the five discussed in this review where the circulating concentrations have been shown to correlate with both cancer risk and metastatic potential; moreover, the epidemiological support for a negative effect of adiponectin on tumorigenesis contrasts with the results of experimental studies of leptin (129), HB-EGF (91), and IL-6 (86) which demonstrated positive paracrine and autocrine activities of these growth factors when they are produced not by surrounding adipose tissue, but by the tumor cells themselves.

Studies are now needed to determine the biological significance of the adipokines when they are produced locally by adipose tissue surrounding the prostate cancer cells. The anatomical situation differs from that in breast cancer because the tumor cells are separated from ready access to a mass of adipose tissue until they have breached the prostatic capsule, whereas breast cancer cells are surrounded by the adipocytes and adipose stromal cells which are an integral part of the breast tissue. Once extension beyond the capsule occurs, leptin, HB-EGF and IL-6 may all act on the prostate cancer cells to enhance their further growth and invasion, either directly or by acting in concert with adipocyte-derived VEGF to stimulate tumor-supporting angiogenesis.

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